PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Artcle 36 and Rule 70)

Applicant's or agent's file reference PCA40739-HMY -SJ	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. **PCT/KR2004/002625**	International filing date *(day/month/year)* **14 OCTOBER 2004 (14.10.2004)**	Priority date *(day/month/year)* 16 OCTOBER 2003 (16.10.2003)

International Patent Classification (IPC) or national classification and IPC

C12N 15/70(2006.01)i

Applicant

HANMI PHARM. CO., LTD. et al

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ (sent to the applicant and to the International Bureau) a total of 3 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) _____, containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:
   - ☒ Box No. I Basis of the report
   - ☐ Box No. II Priority
   - ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☒ Box No. VIII Certain observations on the international application

Date of submission of the demamd	Date of completion of this report
16 AUGUST 2005 (16.08.2005)	06 JANUARY 2006 (06.01.2006)
Name and mailing address of the IPEA/KR Korean Intellectual Property Office 920 Dunsan-dong, Seo-gu, Daejeon 302-701, Republic of Korea Facsimile No. 82-42-472-7140	Authorized officer SHIN, Weon Hye Telephone No. 82-42-481-5591

Form PCT/IPEA/409 (cover sheet) (April 2005)

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/KR2004/002625

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
   - ☐ This report is based on translations from the original language into the following language _____, which is the language of a translation furnished for the purposes of:
     - ☐ international search (under Rules 12.3 and 23.1(b))
     - ☐ publication of the international application (under Rule 12.4)
     - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this reort as "originally filed" and are not annexed to this report):*
   - ☐ the international application as originally filed/furnished
   - ☒ the description:
     pages 1-24 as originally filed/furnished
     pages* _____ received by this Authority on _____
     pages* _____ received by this Authority on _____
   - ☒ the claims:
     pages _____ as originally filed/furnished
     pages* 25-27 as amended (together with any statment) under Article 19
     pages* _____ received by this Authority on _____
     pages* _____ received by this Authority on _____
   - ☒ the drawings:
     pages 1-9 as originally filed/furnished
     pages* _____ received by this Authority on _____
     pages* _____ received by this Authority on _____
   - ☐ the sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. ☒ The amendments have resulted in the cancellation of:
   - ☐ the description, pages _____
   - ☒ the claims, Nos. 4, 6-10, 19, 21-33, 37-40,
   - ☐ the drawings, sheets _____
   - ☐ the sequence listing *(specify)* : _____
   - ☐ any table(s) related to sequence listing *(specify)* : _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages _____
   - ☐ the claims, Nos. _____
   - ☐ the drawings, sheets _____
   - ☐ the sequence listing *(specify)*: _____
   - ☐ any table(s) related to sequence listing *(specify)* : _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/KR2004/002625

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-19	YES
	Claims	none	NO
Inventive step (IS)	Claims	1-19	YES
	Claims	none	NO
Industrial applicability (IA)	Claims	1-19	YES
	Claims	none	NO

2. Citations and explanations (Rule 70.7)

Reference is made to the following documents from the International Search Report (ISR).

D1: US 5,648,237 A (GENENTECH, INC.) 15 JULY 1997
D2: Protein Expr. Purif., Vol. 26(2), pp. 309-320 (NOVEMBER 2002)
D3: WO 2000/015661 A1 (HANMI PHARM. CO., LTD.) 23 MARCH 2000
D4: Appl. Environ. Microbiol., Vol. 64(12), pp. 4862-4869 (DECEMBER 1998)

I. Novelty

The present invention relates to a method for producing an antibody fragment (claim 1), an expression vector (claim 10) and a microorganism (claim 17), which share a technical feature of an expression vector comprising a gene encoding a light chain of an antibody fragment fused with E. coli thermostable enterotoxin signal sequence derivative and a gene encoding a heavy chain of the antibody fragment fused with E. coli outer membrane protein A(OmpA) signal sequence, both of which expression are regulated by a single promoter.

D1 discloses an expression vector comprising genes encoding a light chain domain and a heavy chain domain fused on their 5' ends to the E. coli heat-stable enterotoxin II signal sequence, using dicistronic system; and a method for the high yield production of antibody Fv-containing fragment such as Fab' and F(ab')2 in a microbial secretory system.

D2 discloses a plasmid system comprising a gene encoding a light chain of the antibody fragment fused with the first signal sequence and a gene encoding a heavy chain of the antibody fragment fused with second signal sequence, using dual-promoter system.

D3 and D4 disclose a modified E. coli enterotoxin II signal peptide and an outer membrane protein A signal sequence for the secretion of heterologous protein, respectively.

- continued in Supplemental Box

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

1. Contrary to the requirements of Article 6 PCT, claims 4 & 14 are not properly supported by the description: the E. coli OmpA signal sequence is referred to the SEQ ID NO:23 in claims 4 & 14 but to the SEQ ID NO:24 in the detailed description of the present application(page 9, line 18).

2. Some wording of claim 6 is not proper (Article 6 PCT): "anti-tumor necrosis factor-alpha" in claim 6 should be amended as anti-tumor necrosis factor-alpha antibody.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of:

Box V

There is no prior art document, which directly indicates such a technical feature of the present invention. Therefore, claims 1, 10 & 17 and their dependent claims 2-9, 11-16, 18 & 19 are considered novel fulfilling the requirements set out in Article 33(2) PCT.

II. Inventive Step

The problem to be solved of D2 is same as that of the present invention. However, the solution set out in the present invention is different: neither directly indicated nor fairly suggested in prior arts is the vector featuring a specific combination of a gene encoding a light chain of an antibody fused with E. coli thermostable enterotoxin signal sequence derivative and a gene encoding a heavy chain of the antibody fused with E. coli OmpA signal sequence under the control of a single promoter as recited in claims 1, 10 & 17. No motivation is found in prior arts that one skilled in the art would consider said specific combination. It is also unlikely for the skilled person to arrive at the same solution by a mere aggregation of teachings from D1-D4, especially when the advantage of the present invention appears to be unforeseen over the disclosure of the prior art documents. This requires substantive experiments involving an inventive step.

Therefore, claims 1, 10 & 17 fulfill the criteria set forth in Article 33(3) PCT. Their dependent claims 2-9, 11-16, 18 & 19 also meet the criteria set forth in Article 33(3) PCT.

III. Industrial Applicability

The subject matter of claims 1-19 is considered to be industrially applicable under Article 33(4) PCT.